Robustness of a Cellular Automata Model for the HIV Infection [1]

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Abstract

An investigation was conducted to study the robustness of the results obtained from the cellular automata model which describes the spread of the HIV infection within lymphoid tissues [1]. The analysis focussed on the dynamic behavior of the model when defined in lattices with different symmetries and dimensionalities. The results illustrated that the three-phase dynamics of the planar models suffered minor changes in relation to lattice symmetry variations and, while differences were observed regarding dimensionality changes, qualitative behavior was preserved. A further investigation was conducted into primary infection and sensitiveness of the latency period to variations of the model's stochastic parameters over wide ranging values. The variables characterizing primary infection and the latency period exhibited power-law behavior when the stochastic parameters varied over a few orders of magnitude. The power-law exponents were approximately the same when lattice symmetry varied, but there was a significant variation when dimensionality changed from two to three. The dynamics of the three-dimensional model was also shown to be insensitive to variations of the deterministic parameters related to cell resistance to the infection, and the necessary time lag to mount the specific immune response to HIV variants. The robustness of the model demonstrated in this work reinforce that its basic hypothesis are consistent with the three-stage dynamic of the HIV infection observed in patients.

Key words: HIV infection, cellular automata, spatial structured model
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1 Introduction

Since the first cases of *Acquired Immunodeficiency Syndrome* (AIDS) were notified during the early 1980s, considerable advances have been made in understanding the dynamics of the infection generated by the *Human Deficiency Virus* (HIV). What differentiates HIV from many other viruses is its ability to remain in the system after primary infection. Although the infectious process varies from patient to patient, a typical infection pattern has been observed amongst patients [2,3] and exhibits three phases: primary infection, the latency period and the onset of AIDS. Primary infection is characterized by a broad viral dissemination, which declines markedly (without eliminating the virus)in weeks to months after the emergence of the first HIV-specific immune response [4]. This rapid decrease in the plasma viremia titer is followed by the *clinical latency* period, which may vary from 2 to 10 years or more, with a very low viral burden. During the clinical latency period, although many patients are usually asymptomatic, all suffer a gradual performance deterioration of the immune systems, manifested by the decrease of $CD4^+$ T cell counts [2] to very low concentrations. The onset of AIDS is associated to achieving very low thresholds of $CD4^+$ T cell counts corresponding to 20-35% of the regular values of a normal individual. In the absence of treatment, the outcome of this stage is death by opportunistic diseases.

The main target of the HIV is the $CD4^+$ T cell. The viral envelop protein binds to some specific cell receptor, thus enabling the virus to deposit its genetic material into the cell. Once inside, it uses the host cell machinery to make copies of its viral DNA in the same manner as other retroviruses [5]. When the host cells are able to produce both the DNA and the viral protein envelop, they are able to release new viral particles into the extra-cellular environment. Replication of HIV is extremely fast and mutation rates are very high. It is estimated that during the HIV reproduction process, two generations are produced per week with one mutation per generation [5]. Part of the new strains would be recognized by previously developed immune responses, but part of the variants would not be recognized and would activate new specific immune responses to them. Since the virus is not eliminated, the process of continuously activating a new specific immune response is maintained indefinitely, thus placing stress on the immune system. The ultimate manifestation of the

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effects of this stress is a decline in T cell counts. Several mechanisms have been proposed to explain the decline of T-cell counts [2,6] the aggregation of infected and non-infected cells in the lymphoid tissues (syncytia formation), the destruction of memory-T cells, programmed cell death associated to lymphocyte activation instead of cell proliferation, and high viral replication and mutation rates. However, despite all efforts to determine the cause of this decline during recent decades, the question still remains open-ended.

Over the past two decades many mathematical models based on differential equation approaches have been proposed in order to study the different aspects involved in the development of the HIV infection [7]. Most of these models however, describe the evolution of the virus and cell populations in a compartmentalized manner, and do not take into account the spatial localization necessary to mount the specific immune responses [5]. Although this kind of approach has contributed to the understanding of different aspects of HIV infection dynamics, it has not been able to reproduce the entire three-stage dynamics observed in infected patients. Depending on the adopted approach, the model only adequately describes either the early (stochastic models) or later stages (deterministic models) of the dynamics [7]. There is also a chance it may describe the two time scales using different sets of parameters for different stages [8]. Discrete approaches based on binary cellular automata have also been proposed [9] to describe the interactions amongst $CD4^+$ and $CD8^+$ T cells, macrophages and viral particles. These models reproduce the different attractors of the dynamics [10] or the early stages of the infection [9] but not its entire course. Nowadays, spatially structured models are being recognized as a step forward in understanding the dynamics of virus infection processes, in which the influence of local dispersal of the virus and virus-target cells is relevant for disease persistence in vivo. This is the case of the HIV infection [11,12].

Recently, two of the authors have proposed a two-dimensional stochastic cellular automata (CA) model in order to describe the spread of the HIV infection [1], and which takes into account the spatial localization of target cells (T cells) that occurs in the lymphoid tissues to mount the specific immune response. In the case of the HIV infection it is this localization that contributes to the spread of infection throughout the cells. The model illustrates that the combination of the timescale involved in the immune response of any (healthy) individual with fast replication and high mutation rates of the HIV, together with the spatial localization generated in the lymphoid tissue, may go some way to explaining the three-stage dynamics observed in experimental findings [2,3]. By reproducing the two timescales observed in the experimental data (concerning T cell counts and viremia titer) the model permits the possible mechanisms underlying the dynamics of this infectious process to be investigated. The results suggest that the slow timescale is associated to the agglutination of infected cells in structures, which may compromise the entire

tissue and trap healthy cells, leading to the onset of AIDS. All these structures may be associated to syncytia formation. Syncytia are structures, which are formed when infected blood is mixed with healthy blood, in *in vitro* experiments. Therefore, results suggest that what is observed *in vitro* may also occur *in vivo*.

The cellular automata model proposed in reference [1] is defined on a two-dimensional square lattice so as to mimic the structure of lymphoid tissues where cell interactions take place. In the case of HIV infection, lymph nodes play a major role within lymphoid tissues. The lymph nodes are small organs exhibiting a bean shape. From electromicrography images [13] the region where the interactions between the different cells and the viruses take place, has a fractal structure similar to that of a sponge. The cells take in the order of hours to cross the lymphoid tissue and find the right place to interact within the porous structure. In the model, the range of interaction between the cells is approximated by a surface using a square lattice. Despite the approximation and remarkable accuracy of the model in describing the two timescales and the three-stage dynamics, the question concerning the relevance of the lattice geometry as well as its dimensionality (2-D, 3-D or fractal) remains an important issue to be investigated. This issue was taken up and addressed by Figueirêdo [14] whose results are for the first time reported in this paper. Recently, Omerond [15] conducted a similar investigation into how different tilings of square and cubic lattices, and definitions of the nearest neighbors qualitatively affect the dynamics of the system, without exploiting the robustness. However, while being a more qualitative investigation, it was less detailed than the current study.

Below, further results will also be presented concerning the robustness of the dynamics of the model when varying the stochastic parameters of the model. To be more precise, studies were undertaken into the characteristic changes of the primary infection, due to variations of the initial HIV concentration for both the two and three-dimensional models. Moreover, an analysis was carried out of the time-scaling behavior of the clinical latency period based on the probability that newly infected cells enter the system throughout time, by different lattices. In order to complete the analysis of the cubic lattice, an investigation was also conducted into the behavior of the average latency period as a function of the parameters that governs the intensity and the time delay to mount a specific immune response.

This paper is organized as follows: In section 2, the model is presented together with a discussion of the modifications introduced in order to deal with the triangular and cubic lattices. In section 3, the obtained results are presented and discussed, and the conclusions are presented in section 4.

2 The Cellular Automata Model

In the CA model [1] a target cell (T cells or monocytes) is associated to each site of a square lattice. Each cell is represented by a four-state automaton corresponding to different states of the cell: *healthy*, *infected-A*, *infected-B* and *dead*. The infected-A state corresponds to a virus-producing cell, which promotes the spread of the infection during a time interval τ without any suppression. τ corresponds to the period of time necessary for the immune system to mount a specific immune response to a given virus strain. A virus-producing cell that was already recognized by the immune system is then represented by the infected-B state. Although infected-B cells are less effective than infected-A in contaminating healthy cells, a high concentration in a given region may disseminate the infection throughout the nearby uninfected cells. The infected-B cells eliminated by the cytotoxic mechanisms of the specific immune response or the cytophatic effects of virus replication are represented by the dead state. The high ability of the immune system to replenish depleted cells is taken into account by converting a fraction p_{repl} of the dead cells into new cells. Such new cells mimic the flux of incoming cells from other compartments. Most of the new incoming cells would be healthy, but a (small) fraction of them (p_{infec}) would be infected-A, corresponding to virus-producing cells coming from other compartments.

Simulations were carried on a $L \times L$ square lattice starting from an initial configuration composed of healthy cells, with small fraction, p_{HIV}, of infected-A cells randomly distributed among the healthy cells, representing the initial contamination by HIV. Periodic boundary conditions were considered and each time step corresponded to the parallel updating of the entire lattice according to the following rules:

1) A healthy cell becomes an infected-A if it has at least one infected-A cell amongst its nearest neighbors, or at least $R = 4$ neighbors in infected-B state. Otherwise it remains healthy.
2) An infected-A cell remains in this state during τ time steps, after which it becomes infected-B.
3) An infected-B cell becomes a dead cell in the next time step.
4) A dead cell is replaced by a healthy cell with probability $(1 - p_{\mathsf{infec}})\, p_{\mathsf{repl}}$, or by an infected-A cell with probability $p_{\mathsf{repl}}\, p_{\mathsf{infec}}$, otherwise it continues in the dead state with probability $(1 - p_{\mathsf{repl}})$.

Some of the parameter values chosen are based on experimental findings. For example, one in 10^4 to 10^5 cells in the peripheral blood of infected patients expresses viral proteins [16] during the latency period, and p_{infec} values are brought about by this finding. The probability of replacing dead cells by new incoming cells (p_{repl}) could vary between zero and one and may also vary

from patient to patient. In the original model it was assumed that $p_{\mathsf{repl}} = 0.99$ corresponds to a high replenishment capacity of the immune system, which in this case is not affected by the HIV infection, and is contrary to certain assumptions cited in the literature. Such a replenishment concerns to the population of cells that was recruited or committed do participate in the immune response. Finally, the small fraction p_{HIV} of infected cells randomly distributed in the initial configuration was chosen according to experimental findings, which indicates that one in 10^2 to 10^3 cells harbor viral DNA during primary infection [17,18].

According to the updated rules adopted since the beginning, infection is disseminated in a deterministic manner, driven by cell-cell contact, but eventually newly infected cells are introduced to the system due to stochastic rule 4. Rule 4 accounts for all mechanisms governing the (re)infection process, such as the presence of quiescent infected cells or infected cells coming to other compartments.

In order to investigate the role of lattice symmetry and its dimensionality on CA model dynamics, studies were conducted for the models on the triangular (2D) and cubic (3D) lattices, to compare results with those previously obtained using the square lattice. For such cases, few changes should be made to the rules regarding the neighborhood, as described above:

- Triangular lattice:
  Each site possessed six neighbors, and $R = 3$ was assumed as the minimum number of infected-B neighboring cells required to disseminate the infection, i.e., following the same criteria adopted for the square lattice, this number would correspond to half the number of neighbor sites.
- Cubic lattice:
  Each site possessed twenty six neighbors, hence $R = 13$ was assumed as the minimum number of infected-B neighboring cells required to to infect a healthy cell.

To test the robustness of the model's dynamic behavior regarding the variation of stochastic parameters, the position and fraction of the infected cells at primary infection peak were measured, together with the duration of the latency period when varying respectively, p_{HIV} and p_{infec}, over wide intervals. The sensitivity of the latency period was also measured in the three-dimensional model, when changing the deterministic parameters R and τ. These results are presented and discussed throughout the following section.

3 Results and discussion

In order to analyze the effects of the changes in the symmetry of the lattice, an average three-stage pattern was obtained that emerged from the CA model defined on the triangular and square lattices for $L = 900$ and the same set of parameters used in the original model [1]: $p_{\mathsf{HIV}} = 0.05$, $\tau = 4$, $p_{\mathsf{repl}} = 0.99$, $p_{\mathsf{infec}} = 10^{-5}$. The results shown in figure 1 were an average of 1000 samples (initial configurations) corresponding to different individuals. Hereafter the error bars shown in the plots of all figures indicate one-standard deviation.

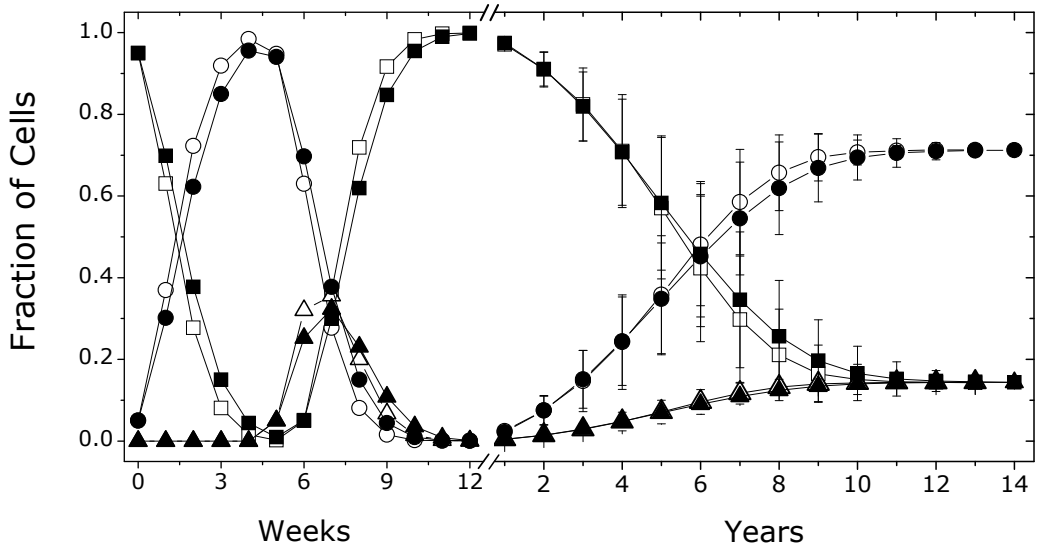

Fig. 1. Time evolution of the fractions of healthy (squares), infected-$A + B$ (circle) and dead (triangles) cells. Solid symbols correspond to the results of the triangular lattice model ($R = 3$), while open symbols refer to the square lattice model ($R = 4$).

As can be observed, there are no major quantitative changes in the patterns obtained for the two lattices (square and triangular), indicating that the three-stage dynamics is quite independent of the lattice symmetry. Figure 2 compares the results obtained from the model defined on the cubic and square lattices. Except for the changes in L and R, all parameters were those adopted in ref [1]. It is worth observing that when the results for different dimensions were compared, significant timescale changes were observed. However, qualitative behavior remained the same in both cases. The differences of the three-dimensional results in relation to those of the two-dimensional were: a one week shift in the peak of the primary infection phase, and a reduction in the duration of the latency period. The duration of the latency period is estimated for each patient by calculating the time necessary for the fraction of healthy cells to achieve a threshold of $\sim 30\%$ after the primary infection. In this manner it was possible to estimate the point that corresponds to the onset

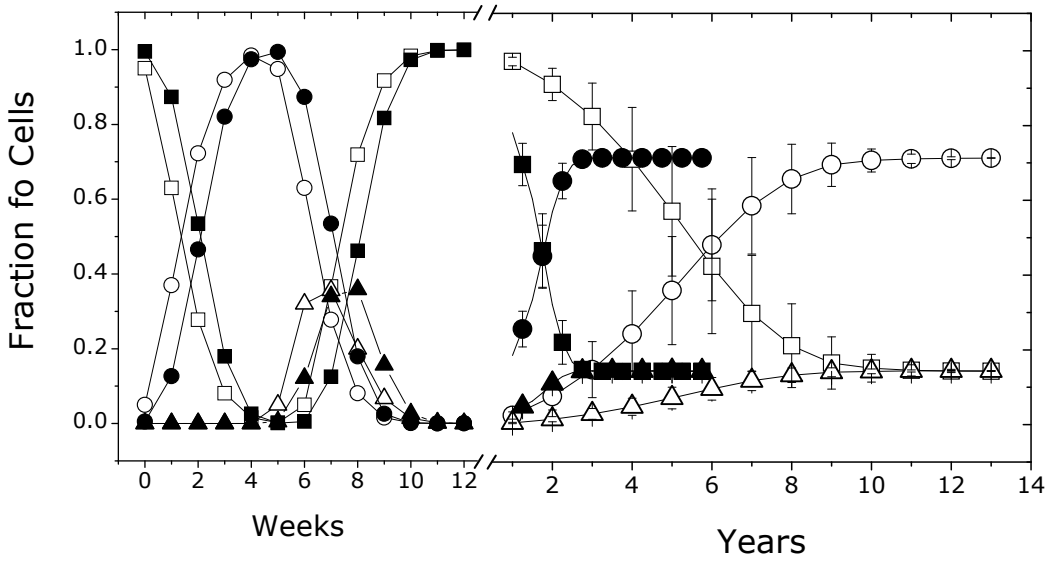

Fig. 2. Time evolution of the fractions of healthy (squares), infected $A + B$ (circle) and dead (triangles) cells. Solid symbols correspond to the results obtained for the cubic lattice with $L = 300$ and $R = 13$ while open symbols correspond to the square lattice using $L = 900$ and $R = 4$. The parameters are those adopted to obtain Figure 1.

of AIDS [2]. The average length of the latency period (in over 1000 samples) was reduced from 7 (2-D) to 2 years(3-D). A decrease in the error bars magnitude was also observed. This result is easily understood when considering the number of neighbors in the different lattices. While the cubic lattice possessed 26 nearest neighbors, the square and triangular lattices possessed 8 and 6 neighbors, respectively. Hence, the large number of neighbors in the 3D case will favor a much faster dissemination of the infection, when compared to the 2D lattices, thus reducing the latency period. When considering the lymphoid tissue as a fractal object, according to the results of this study, the fractal dimension should be closer to two, thus validating the approximation of a two dimensional lattice adopted in the original model [1]. The robustness of the dynamics of the CA model during primary infection was also investigated for variations of the initial concentration of infected cell (p_{HIV}) for 2D and 3D versions of the model. Figure 3 and 4 respectively, on a logarithmic scale, reveal the behavior of two quantities that characterize the primary infection phase: the average maximum concentration of infected cells $< D_i >$ and its position $< t >$ (in time steps) as a function of p_{HIV}. The small error bars indicate the robustness of the results irrespective of the lattice dimensionality. Power-law behavior was observed, indicating $< D_i > \sim (p_{\mathsf{HIV}})^{\alpha}$ and $< t > \sim (p_{\mathsf{HIV}})^{\beta}$ with exponents $\alpha = 0.48 \pm 0.01$ for two-dimensional square and triangular lattices and $\alpha = 0.29 \pm 0.01$ for the cubic. These values of α are related to the average distance between first-nearest-neighbors infected-A cells in the initial configuration, which by it turn scales with $1/D$. Each infected-A cell of the initial configuration produces a pulse of infected cells, of width $(\tau + 1)$ propagat-

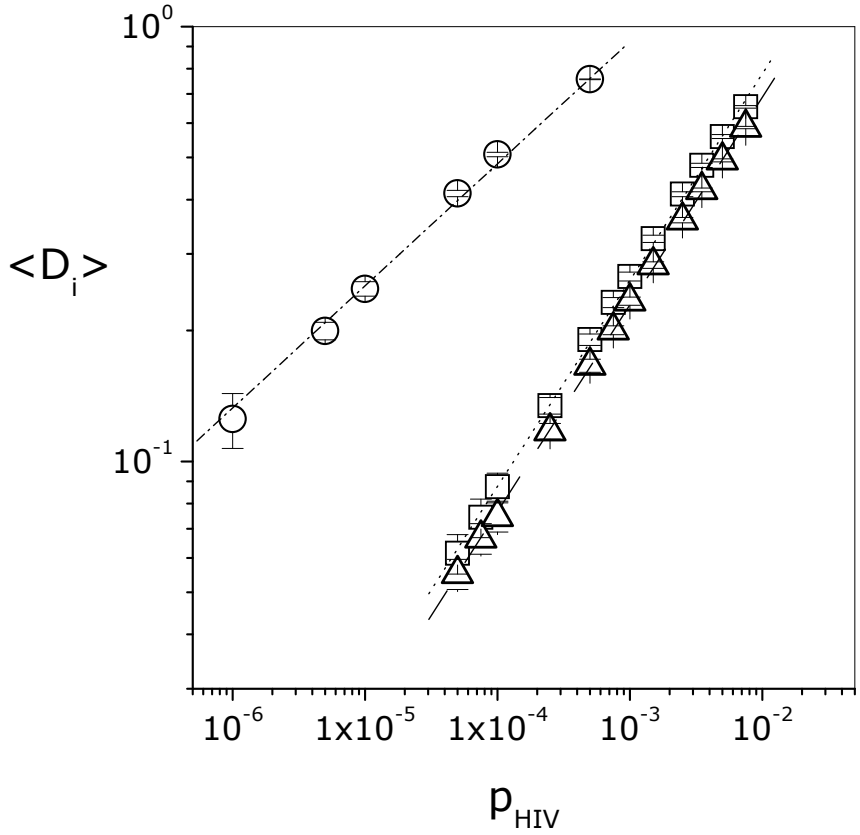

Fig. 3. Average maximum fraction of infected cells during primary infection as a function of p_{HIV}. The different plots correspond to: cubic (◯), square (□) and triangular (△) lattices. The results were an average of over 1000 samples the error bars being of the order of the symbol size. Dashed lines indicate the linear fitting.

ing in all directions. Whenever such average distance is less than or equal to $(2\tau + 1)$, the independent pulses achieve a maximum coverage of the lattice, which corresponds to a maximum of $< D_i >$. The values obtained for β are similar for the two-dimensional lattices: $\beta = 0.44 \pm 0.01$, but a decrease was recorded of 0.30 ± 0.02 for the cubic. In other words, the primary infection peak becomes broader with the decrease of height by one order of magnitude while p_{HIV} varies over two decades for two-dimensional lattices and three decades for three-dimensional. Other authors have claimed that there exists a lack of robustness of the CA model when describing primary infection [19]. However, the results of this study assert the robustness of the results obtained with respect to variations of the minimum concentration of infected cells necessary to launch the infection process. The claim was based on an unproven assumption of exponential growth of the viremia titer in the very beginning of primary infection, and on speculative values for the minimum amount of virus necessary to launch the contamination of an individual, inferred from a few clinical cases. This study illustrates that the same dynamics are launched for a wide range of the initial concentration of infected cells.

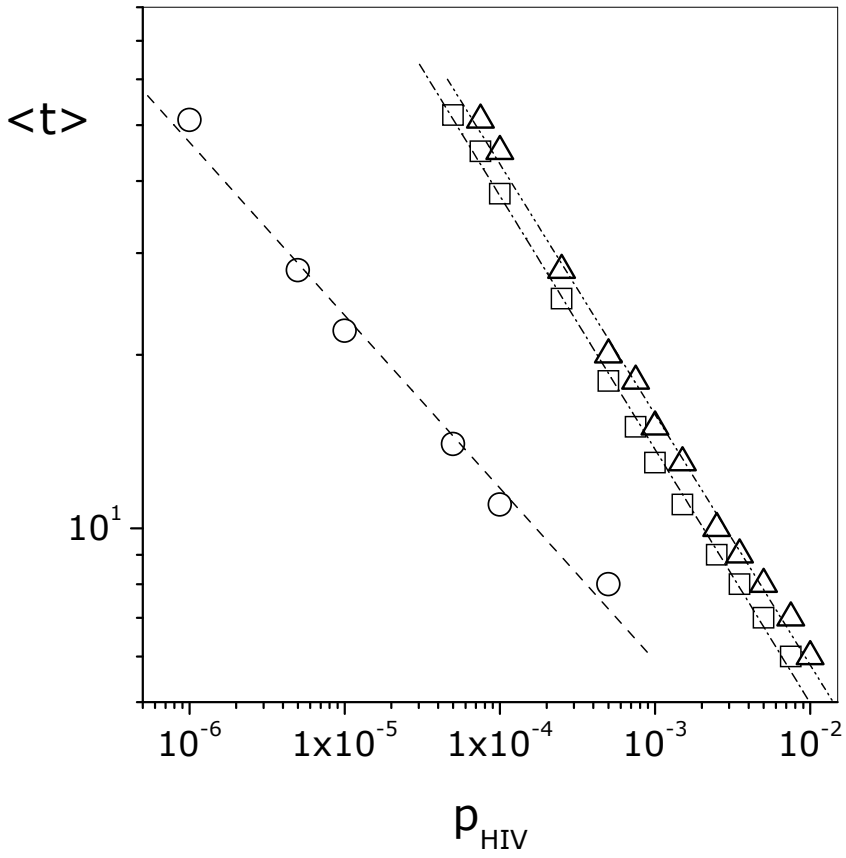

Fig. 4. Average position of the maximum fraction of infected cells achieved during primary infection ($< t >$) as a function of p_{HIV}. Symbols represent the same lattices as described in Figure 3 and the calculation of averages and error bars also follows the same procedures as in the previous figure. Dashed lines indicate the linear fitting.

The average latency period was also investigated as a function of the probability of newly infected cells entering the system ($p_{\mathsf{repl}} \times p_{\mathsf{infec}}$). Since the hypothesis was adopted that the function of the immune system is not affected by the infection, and the replenishment of healthy cells by the bone marrow is maintained constant ($p_{\mathsf{reg}} = 0.99$), we have plotted the average latency period solely as a function of p_{infec}, as shown in figure 5. The behavior of the average latency period is similar for both the triangular and square lattices, but is different in the case of the cubic lattice. The power law exponent γ associated to the average latency period is 0.40 ± 0.01 for square and triangular lattices, and 0.25 ± 0.01 for the cubic.

As previously mentioned, when the same set of parameters (except of L and R) are taken and the dynamical behavior exhibited by the two and three-dimensional models is compared, a significant reduction of the average latency period can be observed. Recently, Solovey et al.[20] investigated how the variations on the deterministic parameters change the dynamics of the model in the

square lattice. To complement the analysis concerning the differences between the two and three dimensional models, this study investigated the behavior of the average latency period in the three-dimensional model when varying R and τ. The results in figure 6(a) indicate that, as in the case of the square lattice [20], the average latency period is not significantly altered due to variations in the time-lag parameter τ. However, when parameter R varies from 9 to 18 an increase in the latency period is observed to the order of 40 weeks, as displayed in figure 6(b). Such an increase corresponds to a decrease in the probability of the occurrence of infected cells and concomitant compact structures leading to long latency periods, as would be expected. It can be noticed that both plots of figure 6 exhibit large fluctuations. Such fluctuations are related to the intrinsic width of the latency period distribution and not with the number of simulations. In fact, fluctuations are governed by the spatial- and *time-dependent* probability of the appearance of compact structures, and the latency period is related to the average distance of such structures, which becomes proportional to the inverse of the cubic ratio of the concentration ρ ($\sim \rho^{-1/3}$) for the three-dimensional lattice.

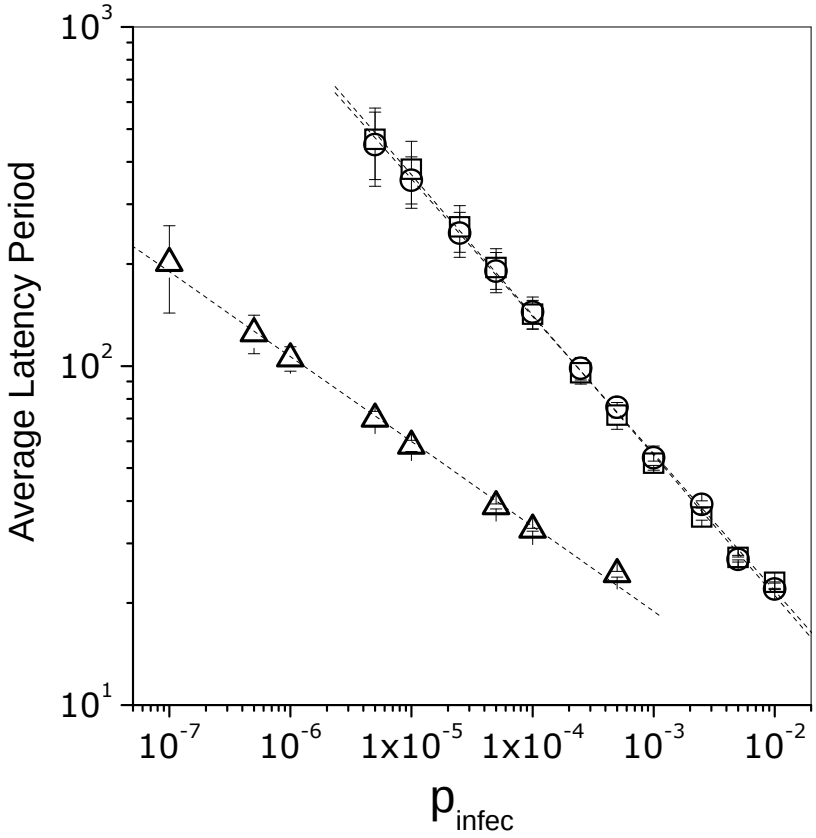

Fig. 5. Average clinical latency period as a function of p_{infec}. The different plots correspond to: cubic (◯), square (□) and triangular (△) lattices. Results were an average of over 1000 samples. Dashed lines indicate the linear fitting.

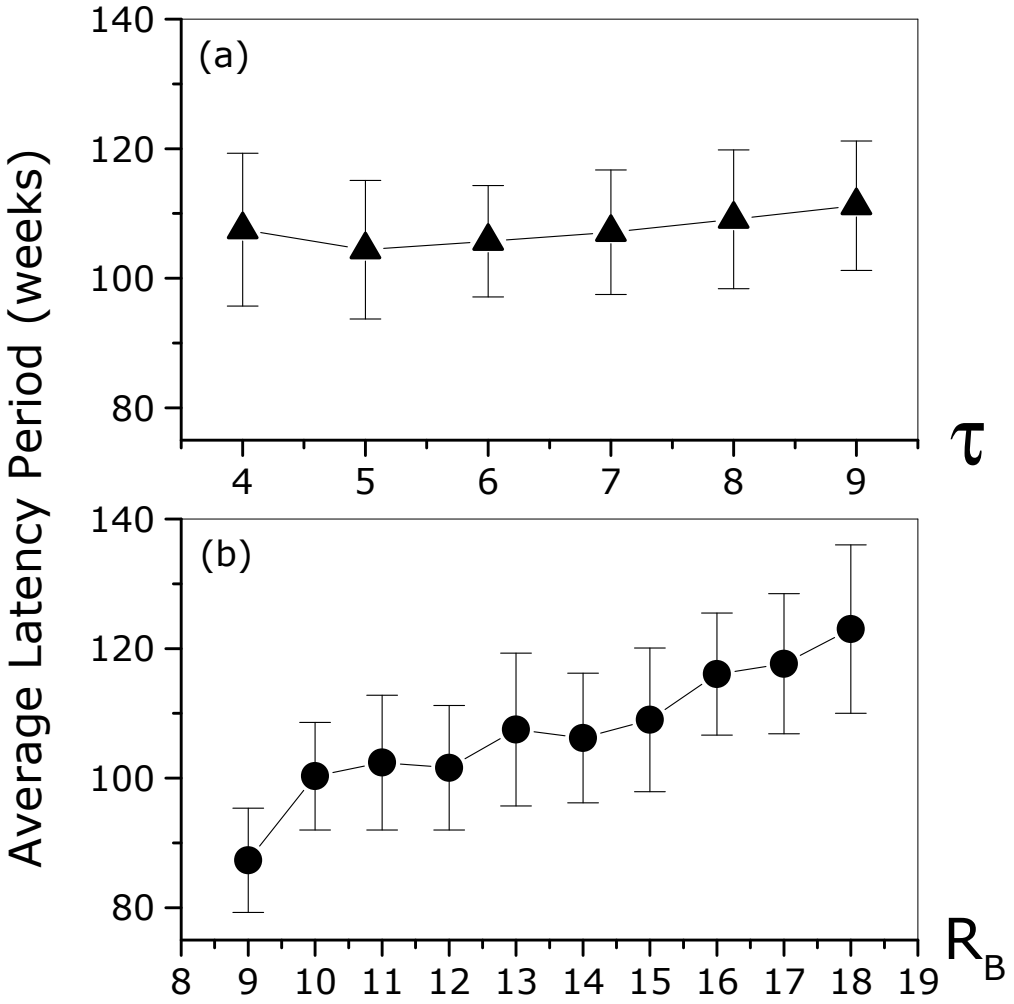

Fig. 6. Average clinical latency period for the cubic lattice model: (a) as function of τ; (b) as a function of R. Results were averaged over 50 samples, using $L = 300$.

4 Conclusions

This paper has analyzed the robustness of the cellular automata model proposed in reference [1] to describe the HIV infection with respect to changes in lattice symmetry and dimensionality and in variations of the stochastic parameters of the model. It has been shown that during the entire course of the infection, the time evolution of the fractions of healthy, infected and dead cells, are quantitatively reproduced irrespective of the lattice symmetry in two dimensions. However, the average latency period was found to be greatly reduced when the lattice dimension changes from two to three, while the primary infection scale and the overall qualitative behavior remains almost unchanged. These results indicate that interactions within the lymph nodes occur on an effective "surface" with a fractal dimension close to two. This therefore ex-

plains the success obtained with the two-dimensional approximation used in the original model.

The robustness of the three-stage pattern was also observed when varying the stochastic parameters associated to the minimum amount of infected cells in the initial configuration necessary to launch the infectious process (p_{HIV}) and to the mechanisms responsible for either incoming newly infected cells or activating quiescent infected cells (p_{infec}). The results indicate quite a remarkable robustness of the three-scale dynamic pattern following power-law behaviors over three orders of magnitude of p_{HIV}. The observed width increase together with the decrease of the primary infection peak, indicates that the lower the initial concentration of infected cells, so the spread of the infection within the tissue is slower and weaker, as would be expected.

The behavior of the average latency period as a function of p_{infec} was also investigated for the three different lattices (square, triangular and cubic). The results also exhibit power-law behaviors over four (2D) to five (3D) decades: the lower the p_{infec} the greater the latency period, since the probability of forming structures associated to the rapid evolution of the onset of AIDS is reduced. In all cases studied, it was observed that the lasting latency period depends on the formation of spatial structures. Once these structures are formed they spreads all over the lattice, thus compromising tissue and trapping healthy cells, as observed in the square lattice model [1]. Such structures could be associated to aggregates of infected cells observed *in vitro* experiments, namely syncytia, and in the lymph nodes of infected patients. Therefore, by means of the robustness analysis, the hypothesis can be validated that the formation of such structures may be responsible for the persistence of the virus in the system after primary infection [3,21]. The appearance of such aggregates, which naturally emerge from the dynamics of the system in the automata cellular model, suggest that a deeper biological investigation should be performed in order to confirm the existence of these structures *in vivo* and their role in the HIV infection.

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